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The 2016 Albert Lasker Basic Medical Research Award: Oxygen sensing—a mysterious process essential for survival

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The 2016 Albert Lasker Basic Medical Research Award honors three physician-scientists: William G. Kaelin, Jr. from Harvard Medical School, Peter J. Ratcliffe from University of Oxford and Gregg L. Semenza, from Johns Hopkins University School of Medicine, for their discovery of the pathway by which cells from human and most animals sense and adapt to changes in oxygen availability, a process essential for survival. The Lasker Award is widely considered as America's most prestigious honor in the biomedical field. For 71 years, this award has recognized the contributions of scientists, clinicians, and public citizens who have made exceptional advances in human health problems. Kaelin, Ratcliffe and Semenza have revealed the core molecular events which could explain how cells tune their physiology to cope with varying quantities of life-sustaining oxygen. These findings might provide novel therapeutics for a wide range of disorders such as anemia, cardiovascular disease, macular degeneration and cancer.

HIF-1: THE HYPOXIC GENES

The journey in the identification and elucidation of molecules critical for oxygen homeostasis started from erythropoietin (EPO). Many creatures use red blood cells to carry oxygen, which serves as a universal electron acceptor in numerous biochemical pathways. When deprived of oxygen, the kidney secretes EPO to stimulate the production of new blood cells from bone marrow. For years, it remains unclear about how cells furnish oxygen supply to control the EPO gene. In early 90's, Semenza and Ratcliffe identified a transcriptional enhancer controlling erythropoietin levels, which vary in response to oxygen concentrations. Placement of this DNA stretch next to other genes renders those genes inducible by low-oxygen conditions. Protein from the nucleus sticks to this DNA-control region, but only when oxygen is scarce. Further, sequence alterations that eliminate protein binding to the DNA obliterate hypoxia-induced gene stimulation. In 1995, Semenza and Wang purified hypoxia-inducible factor 1 (HIF-1) and found that it contains two protein partners, HIF-1α and HIF-1β (Wang et al., 1995). HIF-1α vanishes quickly when cells are shifted from low- to high-oxygen conditions. Under low oxygen conditions, HIF-1 binds and activates target genes such as erythropoietin and vascular endothelial growth factor, which plays a key role in erythropoiesis and angiogenesis respectively. By increasing the new red blood cells and vessels, HIF-1 mediates the adaptive response to hypoxia. In the absence of HIF-1α, vascular development and oxygen-dependent gene expression are severely impaired, leading to embryonic lethality (Iyer et al., 1998). These findings have established HIF-1 as the core molecule of an elaborate physiological network that ensures advantageous responses to oxygen.

HIF-1 DRIVEN GENES

With the discovery of HIF-1 and its binding sequences, Ratcliffe, Semenza and other scientists have rapidly expanded the list of hypoxia-induced genes. In addition to

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EPO and VEGF, HIF-1 binds and activates target genes in many mammalian cells broadly involved in the regulation of metabolism, angiogenesis, embryonic development, immunity and especially cancer. Multiple gene products that mediate the metabolic switch are controlled by HIF-1. Among these genes are *PDK1* gene encoding pyruvate dehydrogenase (PDH) kinase I, *LDHA* gene which encodes lactae dehydrogenase, *LONP* gene encoding a protease that degrades COX4-1, acyl CoA dehydrogenase that generates AcCoA by oxidation of fatty acids, and BNIP3 and BNIP3L which are mitochondrial proteins that trigger mitochondrial-selective autophagy. PDK1 phosphorylates and inactivates PDH which converts glucose-derived pyruvate into AcCoA for entry into the mitochondrial tricarboxylic acid (TCA) cycle. HIF-1 is also essential for hypoxia-induced cell cycle arrest which is the fundamental physiological response to hypoxia. Over-expression of HIF-1 induces G1-phase cell cycle arrest by inhibition of Myc activity and its direct interaction with protein components of the pre-replication complex. HIF-1 activates cyclin genes that cause cancer cells to grow. All these observations have suggested that multiple kinds of cells use HIF-1 to alter numerous genes in response to low-oxygen conditions.

VHL-DEPENDENT MODULATION OF HIF-1

As shown in Figure 1, HIF-1 is stabilized under hypoxic conditions, providing long-enough time for it to enter the nucleus to stimulate the expression of target genes, which promote cells survival in low oxygen conditions. Unearthing how oxygen alters HIF-1 involved one autosomal dominant cancer predisposition syndrome called Von Hippel-Lindau (VHL) disease. VHL disease is characterized by tumors of the brain and spine, retina, kidney, adrenal glands, and several other organs. The next year after purification of HIF, Kaelin, an oncologist who was working on VHLD and variants of gene *VHL*, found that VHL negatively regulates HIF via oxygen-dependent proteolysis (Iliopoulos et al., 1996). VHL protein is a component of a multiprotein complex that bears structural and functional similarity to SCF (Skp1/Cdc53 or Cullin/F-box) ubiquitin ligases. Cells lacking functional VHL protein cannot degrade HIF and thus overproduce mRNAs encoded by HIF target genes. Ratcliffe's group discovered that VHL protein-deficient renal-cancer cells fail to degrade HIF-1α and the other family member HIF-2α (Maxwell et al. 1999). The proteosomal degradation of HIF-1 occurs through the ubiquitin pathway by high-affinity binding to the von Hippel-Lindau E3 ubiquitin ligase.

Subsequent studies led by Kaelin and Ratliffe have revealed that the enzymes called dioxygenases are critical for the recognition of HIF-1 by VHL proteins and its consequent degradation (Ivan et al., 2002; Epstein et al., 2001). These enzymes hydroxylate a highly conserved proline residue in HIF-1α. This oxygen dependent HIF-1α prolyl hydroxylation governs HIF turnover. In the presence of sufficient oxygen, prolyl hydroxylation promotes HIF-1α degradation. As oxygen levels decline, prolyl hydroxylation is rapidly inhibited. An alternative hydroxylation occurs on asparagine residues, which blocks the ability of HIF-1α to recruit transcriptional coactivators. This dual-safety system ensures cells to block any residual HIF-1 escaped from degradation (Lando et al., 2002).

PERSPECTIVES FOR THERAPY

HIF-1 and its relative molecules regulate a group of genes whose products influence a vast variety of biological processes. Manipulating the HIF-1 pathway for therapeutic purposes hence offers a great potential. For example, prolyl

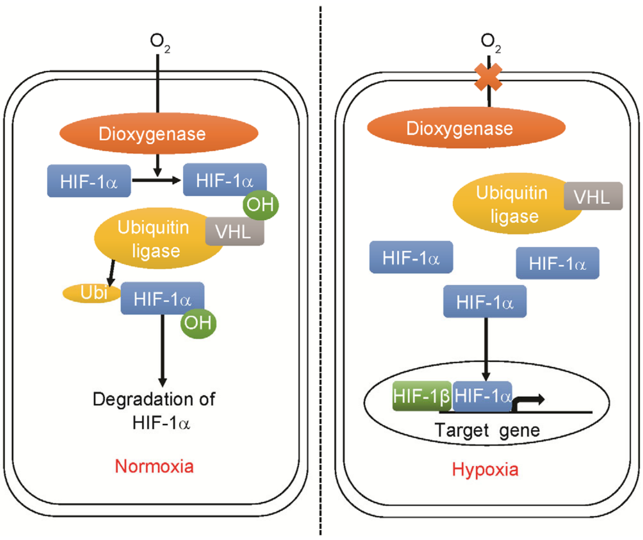

Figure 1 Oxygen-dependent proteolysis of HIF-1.

hydroxylase inhibitors may hold promise for intervention of anemia. Results in both animals and humans have shown that these inhibitors might preserve HIF-1 and stimulate erythropoietin gene activity. Interfering with prolyl hydroxylases might be also effective to counter conditions resulting from inadequate circulation by promoting blood-vessel growth and other adaptations to hypoxia. On the other hand, suppression of HIF-1 provides an alternative approach for control of malignancy because of its capability of blocking angiogenesis. Indeed, a compound that foils HIF-2α is currently in early clinical trials for kidney cancer.

SUMMARY

As cited by Joseph L. Goldstein, a Nobel Laureate and Chair of the Lasker Medical Research Awards Jury, the 2016 Lasker winners combine exceptional insight, creativity, and perseverance in pursuing crucial questions in medical science. This year's Basic Awardees have deepened our understanding of the fundamental pathways by which we sense and respond to the presence of oxygen.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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